REMARKS

This is in response to the official action dated May 9, 2001. Reconsideration in view of the following is respectfully requested.

A request for a three-month extension of time is respectfully requested. The official fee of $460, or any additional extension fees, should be charged to deposit account no. 14-1263.

Additional claim fees in the amount of $159 , or any additional claims fees, should be charged to deposit account no. 14-1263.

The claims stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite. The claims have been revised to overcome the objections by the examiner in paragraph 4 of the action. The examiner is asked to reconsider the spelling of 'cytokinin', which appears to be correct.

Formula I is amended to add oxygen groups on either side of the phosphorus. This is to correct the originally written formula

for ampiphil, as the skilled person would know that the new formula is correct. No new matter is added.

The claims are rejected under 35 U.S.C. 112, first paragraph. The examiner's position is that the specification does not support therapeutic treatment based delivery of any genetic material.

The claims have been clarified as being 'an agent for effecting gene transfer'. The novel discovery of applicant's invention is based on the finding of the important role of DCES (preferably starch, but also gelatin or polymer) in carrying the combined liposome-genetic material complex. It has been surprisingly observed that the drug-containing liposomes are 'piggy-backed' on the starch particles. The liposomes, preferably of the PEG form, interact with the starch particles to keep the starch particles attached while the agent moves through the blood stream. Once the agent reaches the site of embolization, the liposome is released from the starch, and the liposomes become trapped in the tumor and being to release the drug over an extended period of time.

The claims are drawn, not to a gene therapy, but to an agent for effecting gene transfer. Applicant need only demonstrate that the skilled person could make such an agent based on a

complexing of genetic material and liposomes, with a 'piggy-back' support, such as starch. This is shown clearly in the examples. Thought the examples are limited to a single genetic materials combination, the skilled person would understand that merely to form the agent, any genetic material would complex with the liposome, and then the starch. It is noted that certain dependent claims provide specific physical parameters for forming the agent, though based on any genetic material.

Furthermore, it is the aim of the invention to provide an agent, or a vehicle, for delivering a drug. It is not necessary to demonstrate that every drug (genetic material) will be effective in treating a particular illness. Success should be measured by the maintaining of the integrity of the agent. The inventiveness lies in the novel combination of the starch and the liposome, which together act to maintain the drug in bound form until a desired time, such as when the tumor is reached.

While it has been found that certain liposomes (such as PEG, or more preferably MLV PEG) and DCES (e.g. starch) may be preferred, the skilled person would understand from the invention that it is the unique interaction between the liposomes and the DCES that is able to achieve the successful delivery of the drug, regardless of the drug being used. The specification sets forth methods and parameters for constructing the agent.

Therefore, the claims directed to an agent for effecting gene transfer, are supported in the specification, and the rejection should be withdrawn.

Respectfully Submitted,

Bruce S. Londa
Attorney for Applicant
Reg. No. 33,531

Norris, McLaughlin & Marcus P.A.
220 E. 42nd Street, 30th Floor
New York, N.Y. 10017
Telephone: (212)808-0700
Telecopier: (212)808-0844

1. (amended) ~~A pharmaceutical~~An agent for effecting gene transfer, comprising

~~•~~ (a) one or more genetic materials, ~~not encapsulated or encapsulated in~~

(b) liposomes chosen from the group consisting of PEG-liposomes, ~~-~~immuno-liposomes, immuno/PEG-liposomes, cationic liposomes, and ~~optionally~~ polymer-modified liposomes, the genetic materials being not encapsulated or encapsulated therein

~~•~~ (c) a drug carrier embolization system (DCES) comprising one or more chosen from the group consisting of lyophilized or degradable ~~able~~ starch particles ~~and/or~~, gelatin and~~/or~~ polymer particles, ~~such as nanoparticles~~ and

~~•~~ (d) a contrasting agent containing a compound chosen from the group consisting of iodine~~-~~, gadolinium~~--~~, magnetite ~~or~~ and fluorine ~~containing contrasting agents~~.

2. (amended) The agent of claim 1, the genetic materials are chosen from the group consisting of ~~wherein~~ DNA, ~~A~~RNA, ribozyme ~~and/or~~and antisense oligonucleotides ~~are contained as genetic materials~~.

3. (twice amended) The agent ~~of one of the claims~~claim 1, wherein the genetic materials are chosen from the group consisting of therapy genes~~,~~ ~~such as suicide genes, cytokin genes, chemokin genes (MIP1α, MCP)~~, anti-angiogenesis genes~~, such as vascular endothelial growth factor (VEGF)~~, ~~apoptose~~ apoptosis genes~~, such as apoptin, natural born killer (NbK)~~, optionally in combination with marker genes~~, such as green fluorescence protein (GFP), galactosidase gene (LacZ)~~, under optionally inducible, optionally tissue-specific promoters~~, are contained as genetic materials~~.

4. (amended) The agent of claim 3, further comprising ~~wherein the~~ proteins~~,~~ which assist in packing~~s~~ DNA more tightly~~, such as nuclear capsid protein (NCP 7), HMG and/or synthetic substances, such as polyethylene imine, poly L lysine or protamine sulfate, are contained in addition~~.

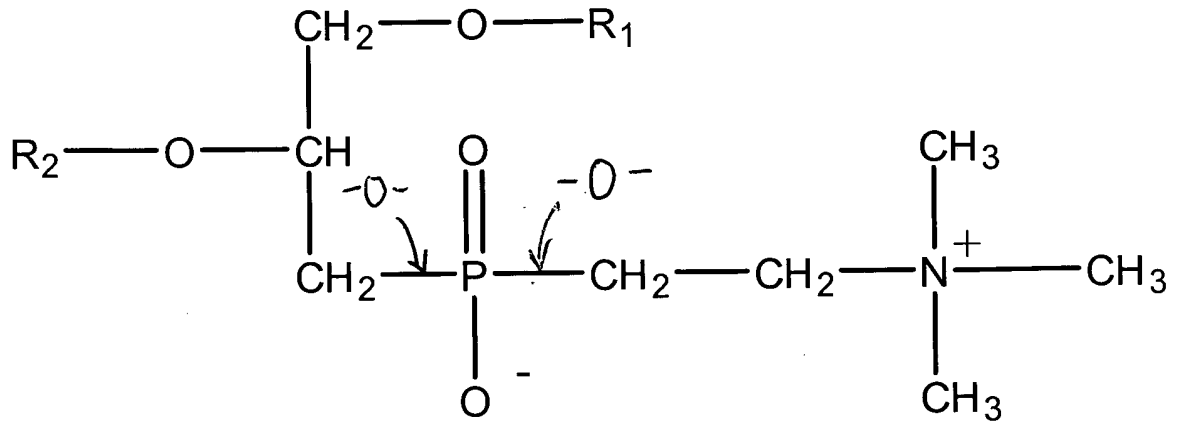
5. (twice amended) The agent of ~~one of the claims~~claim 3, wherein the ~~agent contains the~~genetic material is chosen from the group consisting of suicide genes, herpes simple- virus thymidine kinase gene (HSVtk), deaminase gene, NR/CB1954, pyrine nucleoside phosphorylase and~~/or~~ the cytokinin genes IL-2, IL-4, IL-6, IL-10, IL- 12 and~~/~~IL-15.

6. (twice amended) The agent of ~~one of the claims~~claim 1, wherein the liposomes ~~consist of~~comprise a) a natural, semi-synthetic or completely synthetic amphiphil, b) a steroid, c) a charged lipid component, d) ~~the~~ a water-or lipid-soluble genetic material and/or e) a carrier liquid ~~and optionally additional inert materials.~~

7. (amended) The agent of claim 6, wherein the quantitative ratio of a to b to c ~~preferably~~ is in the molar ratio of 1—: 0.3 : 0.1 to 1 : 1 : 0.1 or 1 : 1 : 0.5 and the molar ratio of c to d is 2 : 1 to 10 : 1.

8. (amended) The agent of ~~claims~~ claim 6, wherein the ~~natural, semi-synthetic or fully synthetic~~ amphiphil ~~preferably~~ chosen from the group consisting of ~~is~~ a lipid, a surfactant, an emulsifier, polyethylene glycol (PEG) ~~or~~ and lipid-PEG.

9. (amended) The agent of claim ~~1~~6, wherein the amphiphil is a compound of the general formula I



(I)

in which R_1 and R_2 represent C_{10} to C_{20} alkanoyl, alkenoyl, alkyl or alkenyl.

10. (twice amended) The agent of ~~one of the claims 6 to 9~~claim 6, wherein the steroid is chosen from the group consisting of cholesterol, diethoxycholesterol ~~or~~ and sitosterol.

11. (twice amended) The agent ~~of one of the claims~~claim 6, wherein the charged lipid
component is chosen from the group consisting of the anion of diacetyl phosphate, of palmitic acid ~~or~~ and of stearic acid~~,~~; the anion of a phospholipid, ~~such as phosphatidyl serine, phosphatid acid or~~; ~~the~~ the anion ~~enzyme~~ of a sphingolipid~~,~~; ~~such as sulfatid, or~~ and polyethylene glycol (PEG~~), such as MPEG-DSPE~~).

12. The agent of claim 11, wherein the charged lipid component is fluorinated.

13. (twice amended) The agent of ~~one of the claims~~claim 6, wherein the ampiphile further comprises~~wherein~~ polymer particles in the form of a 25% aqueous solution of Poloxamer® ~~are used~~ as additional inert materials.

14. (twice amended) The agent of ~~one of the claims~~claim 1, wherein the genetic materials are present in a form chosen from the group consisting of
- ~~SUV~~ (small unilamellar vesicles) PEG liposomes,
- ~~LUV~~ (large unilamellar vesicles) PEG liposomes,
- ~~REV~~ (reverse phase evaporation vesicles) PEG liposomes,
- ~~MLV~~ (multilamellar vesicles) PEG liposomes,
- ~~anti-Ki-67-immune~~ PEG liposomes,
- ~~anti-CEA~~ PEG liposomes ~~or~~and
- ~~PEG~~ DAC-Chol liposomes.

15. (twice amended) The agent of ~~one of the claims 1 to 14~~claim 1, ~~wherein the~~comprising starch particles~~,~~ are lyophilized, and are present in a size of 40 - 90 µm and are in a physiological salt solution in a concentration of 5 to 70 mg/mL.

16. The agent of claim 15, wherein the starch particles have a particle size of 60 to 90 μm.

17. (twice amended) The agent of ~~one of the claims~~claim 1, ~~wherein~~ comprising absorbable gelatin powder ~~is contained~~.

18. (twice amended) The agent of ~~one of the claims~~claim 1, wherein the agent contains phenyl derivatives with one or more iodine substituents as iodine-containing contrasting agent.

19. (amended) The agent of claim 18, wherein the agent ~~contains~~ further comprises one chosen from the group consisting of Iopromide®, Ioxitalamate®, Ioxaglate®, Iopamidol®, Iohexol®, Iotralon®, Metrizamide® ~~or~~ and Ultravis®.

20. (twice amended) The agent of ~~one of the claims~~claim 1, wherein the agent contains fluorinated lipids as contrasting agent.

21. (twice amended) The agent of ~~one of the claims~~claim 1, wherein the agent contains 30 to 90 mg of lyophilized or degradable starch particles and 5 to 100 mg of genetic material, which is or is not encapsulated.

22. (twice amended) The agent of ~~one of the claims~~claim 1, wherein ~~the agent contains~~
(a) the genetic material is LacZ marker gene and ~~the~~ pUT HSVtk suicide gene,
(b) encapsulated in MLV PEG liposome,
~~as~~ (c) the DCES is starch particles~~,~~ being Spherex® or Gelfoam®, and
~~a fluorinated~~(d) the contrasting agent is fluorinated.

23. (twice amended) A method for producing an agent for effecting gene transfer ~~of one of the claims 1~~, wherein 30 to 90 mg of a compound chosen from the group consisting of lyophilized or degradable starch particles ~~and/or~~, gelatin and~~/or~~ polymer particles are dissolved in 3 to 6 mL of contrasting agent and, subsequently, ~~the~~ a therapeutical~~ly~~ ~~necessary~~ amount

of genetic material is added~~.~~, to thereby produce the agent for effecting gene transfer.

24. (twice amended) ~~A~~ The method ~~for producing an agent of~~according to claim 23~~ one of the claims 1~~, wherein ~~the~~ the therapeutic amount of a genetic material and optionally a complexing agent are dissolved in one or more lipids and mixed with the starch particles and ~~a~~ the contrasting agent.

34. (new) The agent of claim 1, wherein the genetic material is encapsulated in MLV PEG, and the DCES is starch particles.

35. (new) The agent of claim 34, comprising 30 to 90 mg of starch particles and 5 to 100 mg of genetic material.

36. (new) The agent of claim 34, wherein the starch particles are of a size 40-90 μm.

37. (new) The agent of claim 1, wherein the polymer particles are nanoparticles.

38. (new) The agent of claim 3, wherein the therapy genes are chosen from the group consisting of suicide genes, cytokin genes and chemokin genes (MIP1α, MCP); the anti-angiogenesis genes are vascular endothelial growth factor (VEGF); the apoptosis genes are chosen from the group consisting of , apoptin and natural born killer (NbK); and the marker genes are chosen from the group consisting of green fluorescence protein (GFP) and galactosidase gene (LacZ).

39. (new) The agent of claim 4, wherein the proteins are chosen from the group consisting of nuclear capsid protein (NCP 7), HMG, polyethylene imine, poly-L-lysine, and protamine sulfate.

40. (new) The agent of claim 11, wherein the phospholipid is chosen from the group consisting of phosphatidyl serine and phosphatid acid; the sphingolipid is sulfatid; and the PEG is MPEG-DSPE.

41. (new) A method for gene transfer and gene therapy of liver metastases; tumors of the lung, bladder, head and neck, urogenitals, lymph nodes, breasts; glioblastoma; arthritis; and asthma, comprising the step of administering a pharmaceutical agent according to the agent for effecting gene transfer of claim 1, intraarterially or locally, whereby a substantial decrease in size of tumor is effected.

42. (new) The method of claim 41, wherein the treatment is for liver metastates, and the agent is administered intraarterially.

43. (new) The method of claim 42, wherein the agent comprises genetic material encapsulated in MLV PEG, and the DCES is starch particles.

44. (new) The method of claim 43, wherein the agent comprises 30 to 90 mg starch particles and 5 to 100 mg of genetic material.

45. (new) The method of claim 43, wherein the genetic material includes pUT 649.

46. (new) A method for the treatment of any of the diseases neurodegenerative and autoimmune diseases; Parkinson's disease, Alzheimer's disease and multiple sclerosis; diabetes type I, diseases accompanying transplantations; restenosis; and high blood pressure; comprising the step of administering as pharmaceutical agent the agent according to claim 1.